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# FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF CEFUROXIME AXETILE

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## ABSTRACT

Floating matrix tablet of cephalosporin antibacterial drug cefuroxime axetil can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F2, F6 gave better-controlled drug release in comparison to the other formulations. The drug release pattern from the optimized formulations was best fitted to Korsmeyer-Peppas model and zero order kinetics. Drug – excipients interaction of optimized formulations was carried out by using FT-IR studies. In this analysis drug – excipients compatibility interactions were not observed.

**Key Words:** cefuroxime axetil, Floating matrix tablet

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## INTRODUCTION

The oral ingestion is the predominant and most preferable route for drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drug. Time controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency leading to improved patient compliance The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from the small intestine. For the successful performance of oral CRDDS the drug should have good absorption throughout the GIT, preferably by passive diffusion In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time.

Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously

releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach. GRDFS can be used as carriers for drugs with so called absorption windows. These substances for example antiviral, antifungal and antibiotic agents (Cephalosporin's, quinolones, penicillin's, sulphonamides, aminoglucosides, tetracycline's etc) are taken up only from very specific sites of GIT. In addition, by continuously supplying drug to its most efficient site of absorption, the dosage forms allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin Low molecular weight, Heparin and Protease inhibitors. Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size. However standard controlled released dosage forms offer only limited advantages for drugs that have an absorption window in the upper small intestinal. (Eg: Levodopa, Furosemide, Riboflavin). Once emptied from the stomach, the passage through this region is rapid, thus limiting the extent of absorption at this site. In order to increase the bioavailability of this type of drugs, the residence time of the controlled-released dosage forms in the upper GIT needs to be prolonged. Oral drug administration is by far the most preferable route for taking medications. However, the therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the intestine. Such pharmacokinetic limitations lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect. This results in "pill burden" and consequently, decreased patient compliance. The phenomenon of absorption via a limited part of the GI tract has been termed the "narrow absorption window"; once the dosage form passes the absorption window, the drug will be neither bioavailability nor effective. In extreme cases, drugs that are insufficiently absorbed due to narrow absorption cannot be delivered entirely, and are either given by a parenteral route or the development of such medication, which is otherwise safe and effective, is stopped altogether. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e. in the stomach and to release the drug in a controlled manner, so as to achieve a zero order kinetics (i.e. "oral infusion") for a prolonged period of time.

Cefuroxime axetil tablets contain cefuroxime as cefuroxime axetil. Cefuroxime axetil is a semisynthetic, broad-spectrum cephalosporin antibiotic for oral administration. Cefuroxime is excreted unchanged in the urine; in adults, approximately 50% of the administered dose is recovered in the urine within 12 hours. The pharmacokinetics of cefuroxime in the urine of pediatric patients has not been studied at this time. Until further data are available, the renal pharmacokinetic properties of cefuroxime axetil established in adults should not be extrapolated to pediatric patients. Cefuroxime is a broad-spectrum antibiotic, cefuroxime axetil has saturation kinetics that could be overcome by slow release of drug from the formulation, by incorporating cefuroxime axetil in sustained drug-delivery system. Cefuroxime axetil has higher absorption in the proximal region of the GI tract and poor absorption as well as antibiotic-associated colitis, when a large amount of drug entered the colon suggest it is an ideal candidate for a gastroretentive drug-delivery system that will prolong the gastric residence time of the dosage form, giving prolonged drug release in the upper GI tract, where absorption of cefuroxime is well confined (1-3).

The present work is aimed at preparing gastric retentive floating matrix tablet formulations of cefuroxime axetil using various low-density polymers. The composition of these formulations will be selected by using trial and error methods. To study the effect of various factors like drug polymer ratio, drug sodium bicarbonate ratio and polymer grade on the parameters like duration of buoyancy and release rate.

## MATERIALS AND METHOD

### Standard graph of cefuroxime axetil

The stock solution was freshly prepared by dissolving 100 mg of cefuroxime axetil in few ml of methanol (5ml) in a 100ml volumetric flask and then make up the solution upto the mark using 0.1N HCl for

obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/mL (stock II). From this secondary stock 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4 mL, was taken separately and made up to 10ml with 0.1N HCl, to produce 4, 8, 12, 16, 20 and 24 µg/ mL respectively. The absorbance was measured at 281 nm using a UV spectrophotometer (Systronic, Ahmedabad, India).

**Preparation method of cefuroxime axetil floating tablets (4-6)**

Cefuroxime Axetil (300 mg equivalent to 250 mg of cefuroxime base) with different polymers The powder blend was then lubricated with magnesium stearate (2%) and talc (1%) mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 12-mm standard flat-face punches.

**Buoyancy / Floating Test**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by a Rosa et al., 1994. Here, the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

**Water uptake studies**

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at 37° $\pm$ 0.5°c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU)

$$\%WU = (Wt - Wo) * 100 / Wo$$

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 60, 120 and 180, 240, 300, 360, 420, 480, 540,600, 660, and 720 minutes. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets, & the mean values were plotted versus time. Each sample was analyzed at 281nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

**RESULTS AND DISCUSSION**

The study started with the construction of standard calibration curve of cefuroxime axetil. The $\lambda_{max}$ of cefuroxime axetil in 0.1N HCl was scanned and found to have the maximum absorbance at 281 nm. Standard graph of cefuroxime axetil in 0.1N HCl was plotted by taking concentration ranging from 4 to 24 µg/mL and a good correlation was obtained with $R^2$ value of 0.9991(Table-1 and Fig-1).

**Table-1 Standard curve for cefuroxime axetil**

| Concentration | Absorbance |
|---|---|
| 0 | 0 |
| 4 | 0.182 |
| 8 | 0.326 |
| 12 | 0.466 |
| 16 | 0.622 |
| 20 | 0.793 |
| 24 | 0.940 |

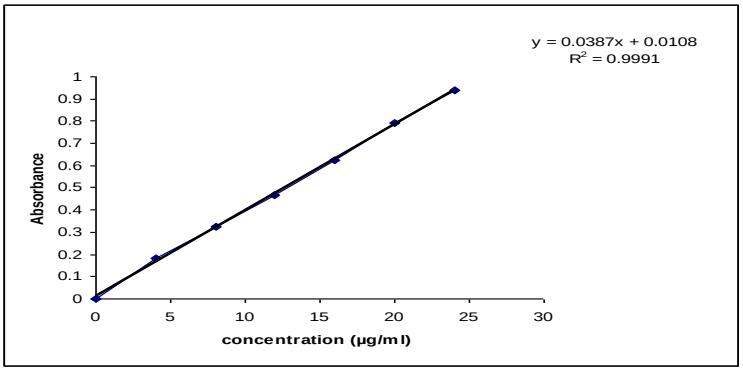


**Fig-1 Standard graph of cefuroxime axetil**

The physical evaluation parameters were also tested. The total weight of each formulation was maintained constant; the weight variation of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 325 mg . Weight of the tablet was fixed at 500 mg and the weight variation for every batch was tested and found within the acceptance limits. Hardness of the tablet was fixed 6 kg/cm$^2$ and was maintained for all the batches in order to minimize the effect of hardness on the drug release because; the effect of polymer concentration is the only area of interest. Tablet thickness was also used to assess the quality of tablets.

Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablets ranged from 4.01 to 4.84 mm and linearly correlated with the weight of the tablets. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 95-98%

***In vitro* buoyancy study**

Further, the formulated tablets on immersion in 0.1N Hydrochloric acid media they remain buoyant for 12 h with lag time of 120 to 180 seconds. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced $CO_2$ that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. Results are shown in table 9. All the batches showed good *in vitro* buoyancy. The results of the *in vitro* buoyancy study of cefuroxime axetil tablets are shown in Fig-2. Finally, lag time was observed less than 3 min for all the formulations and then optimizing the sodium bicarbonate portion at 12% w/w to the total tablet weight. Also the tablet integrity, swelling characteristics were found satisfactory. Floating characteristics like lag time, total floating time for all the formulations were studied and reported in (Table-2).

**Table-2 Floating properties of cefuroxime axetil tablets**

| Formulation code | Lag time (sec) | Total floating time (h) | F13 | 169 | >12 |
|---|---|---|---|---|---|
| **F1** | 126 | >12 | **F14** | 175 | >12 |
| **F2** | 120 | >12 | **F15** | 179 | >12 |
| **F3** | 130 | >12 | **F16** | 185 | >12 |
| **F4** | 136 | >12 | **F17** | 129 | >12 |
| **F5** | 128 | >12 | **F18** | 135 | >12 |
| **F6** | 139 | >12 | **F19** | 144 | >12 |
| **F7** | 146 | >12 | **F20** | 156 | >12 |
| **F8** | 149 | >12 | **F21** | 140 | >12 |
| **F9** | 161 | >12 | **F22** | 142 | >12 |
| **F10** | 172 | >12 | **F23** | 166 | >12 |
| **F11** | 176 | >12 | **F24** | 181 | >12 |
| **F12** | 180 | >12 | **F25** | 176 | >12 |

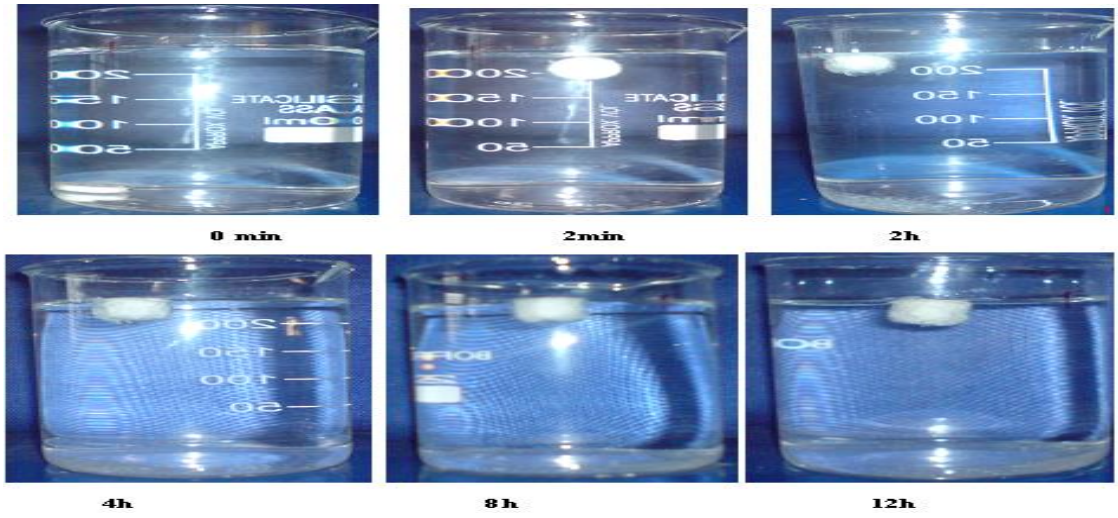


**Fig-2 *In vitro* buoyancy study of cefuroxime floating tablets**

***In vitro* dissolution**

The *in vitro* dissolution testing was performed and the results of the formulations were expressed**.** The release of cefuroxime axetil was studied using USP dissolution apparatus II. The dissolution media were 900 ml 0.1 N HCl maintained at 37 ± $0.5^0$C with rotation speed of 50 rpm. Aliquots of 5 ml was collected at predetermined time intervals and replenished with equivalent volume of fresh medium. The samples were diluted to a suitable concentration with 0.1N HCl and were analyzed by using UV/VIS double beam spectrophotometer at 281 nm. The results are expressed as mean±S.D (n=3). *In vitro* dissolution study of formulations F1, F2, F3 and F4 were done in 0.1 N HCl and the percent of drug release from formulations F2, F3 and F4 was 97.97, 80.05, 74.40 in 12 h respectively, formulation F1 unable to sustain the drug release desired period of time but in case of formulation F2, 97.97% of the drug was released in 12 h, this was considered due to different polymer concentrations in all the four formulations. All these four formulations floated for 12 h. Formulations F3 and F4 failed to drug release profile. Formulation F2 obtained the desired drug release profile and floated with a lag time of 120 sec, for these reasons, it was considered as best formulation among all the four formulations (Fig-3-7).

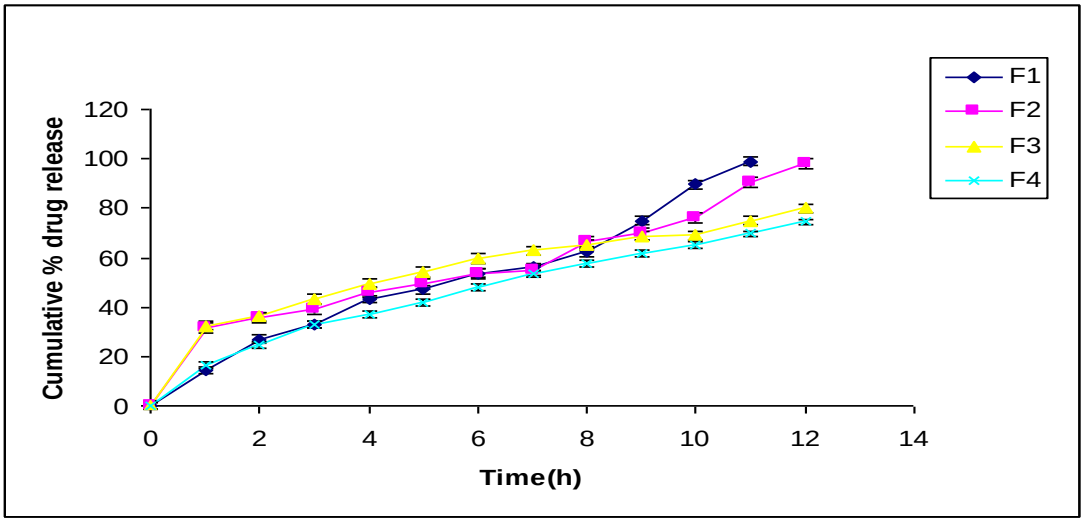


**Fig-3 Cumulative % drug release of HPMC K4M with Lactose Vs Time**

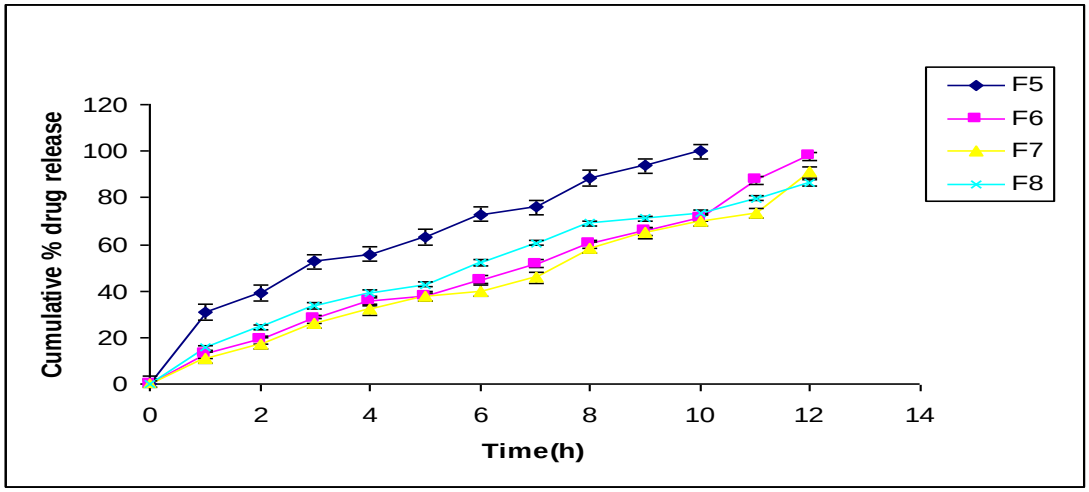


**Fig-4 Cumulative % drug release of HPMC K15M with Lactose Vs Time**

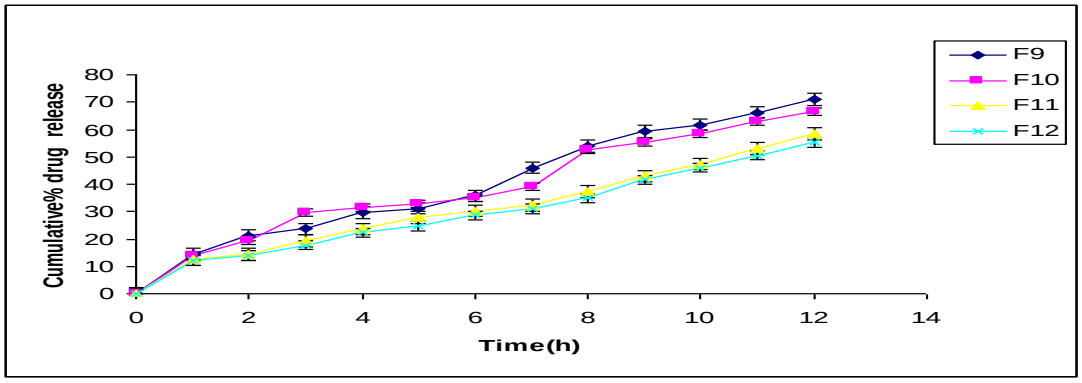


**Fig-5 Cumulative % drug release of HPMC K100M with Lactose Vs Time**

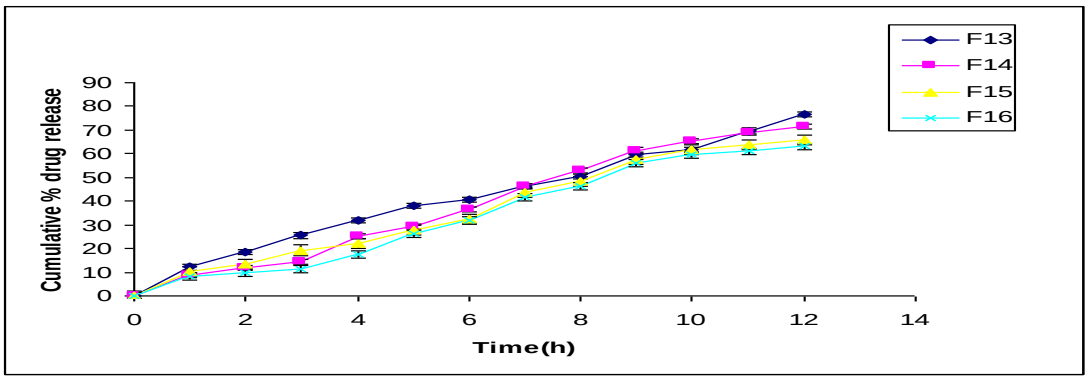


**Fig-6 Cumulative % drug release of sodium alginate with Lactose Vs Time**

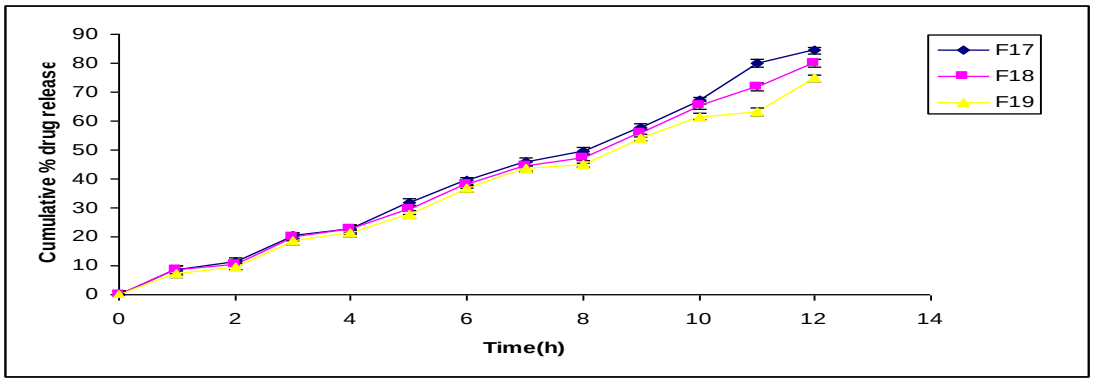


**Fig-7 Cumulative % drug release of HPMC K4M with MCC Vs Time**

**Mechanism of drug release**

The mechanism of release for the optimized formulations was determined by finding the $R^2$ value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the $R^2$ value of Korsmeyer-Peppas and zero-order model is very near to 1 than the $R^2$ values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas and zero-order model mechanism (Table-3).

**Table-3 Release kinetics of optimized fromulations**

| S. No. | Formulation | Zero order | First order | Higuchi | Korsmeyer & Peppas | Peppas (n) |
|---|---|---|---|---|---|---|
| **1** | F2 | 0.974 | 0.684 | 0.898 | 0.994 | 0.57 |
| **2** | F6 | 0.962 | 0.503 | 0.933 | 0.915 | 0.75 |

## CONCLUSION

Systematic studies were conducted using four different polymers in different concentrations to prepare cefuroxime axetil floating tablets. All the prepared systems were evaluated for the different properties. Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness and weight variation, floating lag time, floating time, content uniformity and *in vitro* drug release**.** The formulations containing sodium alginate did not show promising results, however least lag time was optimized, but the drug release was poor, this is due to the conversion of sodium alginate to alginic acid in the acidic medium (pH 1.2) producing a tough and rubbery texture to the tablet. The drug release was further inhibited by sodium .bicarbonate in the alginate matrices. Floating matrix tablet of cephalosporin antibacterial drug cefuroxime axetil can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F2, F6 gave better-controlled drug release in comparison to the other formulations.

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